Remarks

Claims 32 and 34-43 have been canceled without prejudice or disclaimer, and with the understanding that Applicants may pursue the subject matter encompassed by the canceled claims in a continuation application. New claims 44 to 49 have been added. The new claims find support throughout the specification. More specifically, new claims 44 and 45 find exemplary support in Tables 2 to 4. New claims 46 and 47 find exemplary support in Examples 4 to 6. New claim 48 finds exemplary support in Examples 5 to 6. New claim 49 finds exemplary support at page 10, lines 11-12.

No new matter has been introduced by any of the new claims. After entry of the amendments, claims 44 to 49 will be pending.

1. **Rejection under 35 U.S.C. § 103(a)**

The Examiner maintains his rejection of claims 32, 33 and 35-43 as being obvious over EP 0847992 to Suzuki *et al.* ("Suzuki"), and also his rejection of claims 32, 34, 38, 40 and 43 as being obvious over Suzuki in view of the International Cosmetic Ingredient Dictionary and Handbook ("Dictionary") for the reasons detailed in the previous office action.

Applicants respectfully disagree with the Examiner's continued reliance on Suzuki, alone and in combination with the Dictionary, in rendering Applicants' claimed invention obvious. However, in an effort to expedite prosecution of the subject application, Applicants have canceled claims 32 and 35-43, thereby effectively mooting these rejections.

Regarding new claims 44-49, Applicants bring to the Examiner's attention that Suzuki does not disclose pharmaceutical formulations comprising a benzamide derivative of formula (1) in combination with the specific additives as claimed in new independent claims 44 and 46. More generally, unlike the recitation in Applicants' claim 44, Suzuki does not teach or suggest the combination of such a benzamide derivative with an excipient, a lubricant, a disintegrant and an amino compound and/or an inorganic base. Unlike the recitation in Applicants' claim 46, Suzuki does not teach or suggest the combination of such a benzamide with a solvent and a further additive selected from the group consisting of an organic acid salt, an amino compound and an inorganic base. Suzuki merely provides a general laundry list of additives, such as those at page 46, which may potentially be used for pharmaceutical formulations of any sort. Without additional guidance, a person of ordinary skill in the art would not be motivated to prepare the particular formulations claimed by Applicants. Applicants note that Suzuki does not even generally teach the use of an amino compound. While the Dictionary does list exemplary amino compounds, there is no

motivation to combine the teaching of the Dictionary with Suzuki. And even if there were such a motivation, the combination of Suzuki with the Dictionary would clearly not teach or suggest Applicants' claimed formulations.

The Examiner continues to not appreciate the unexpected nature of Applicants' invention – *i.e.*, that select benzamide derivatives, while stable neat, can become unstable when present in a pharmaceutical formulation with other components; and further, that certain excipients in the formulation stabilize the benzamide derivatives while other excipients accelerate their degradation. No one before Applicants has made these observations. Further, Applicants have exploited these findings by preparing pharmaceutical formulations that promote stabilization of these benzamide derivatives. That is why a formulation of a benzamide derivative with a degradation value of, for example, 0.21% (*i.e.*, a D-mannitol formulation) compares favorably to the corresponding control value of 0.18% degradation for the neat benzamide derivative. In other words, the formulation of the benzamide derivative containing D-mannitol is comparably as stable as the neat benzamide derivative. In contrast, a formulation of the benzamide derivative containing lactose has a degradation value of 0.55%, which means that this particular formulation unfavorably accelerates degradation of the benzamide derivative compared to its neat degradation value of 0.18%. The continued stability of the active component, (*e.g.*, the benzamide derivative), in a pharmaceutical formulation is obviously highly desired.

Example 2 of the present application demonstrates that pharmaceutical formulations according to the invention as recited in new claim 44 exhibit superior properties with respect to the stability of the benzamide derivative against degradation compared to comparative samples g, h, and i in Table 3 (from Reference Example 1) and samples a and b in Table 2, all of which are not encompassed by new claim 44. Sample A includes 5.0 mg of active ingredient (*i.e.*, benzamide derivative) and thus cannot be compared to samples b to I, which contain 1.0 mg of active ingredient. However, in comparing the stability data among samples b to i, it is evident from Table 4 at page 13 of Applicants' specification that the "claimed samples" c, d, e, and f exhibit better stability against degradation under both of the storage conditions tested (*i.e.*, 60° C air-tight/4 weeks and 80° C air-tight/3 days) than sample b and the "reference samples" g, h, and i. Under conditions of 80° C air-tight/3 days, samples c, d, e and f show 0.5%, 0.4%, 0.4% and 0.4% degradation products, respectively, while in contrast, samples b, g, h and i show 1.3%, 3.0%, 2.1% and 5.3% degradation products, respectively. Thus, the difference between the "claimed samples" c, d, e, and f (as shown in Table 2 at page 12), and sample b and the "reference examples" g, h, and i (as shown in Tables 2 and 3 at page 12) is that although all samples contain, in addition to the benzamide derivative,

D-mannitol as an excipient, magnesium stearate as a lubricant and carboxymethylstarch sodium or partly pregelatinized starch as a disintegrant, the "claimed samples" contain an amino compound and/or an inorganic base as recited in new claim 44. In contract, sample b and the "reference samples" g, h, and i do not contain such an additional amino compound or inorganic base. For this reason, sample b and the "reference samples" g, h, and i are less stable than the claimed samples in that they produce a higher amount of degradation products. Therefore, Example 2 clearly demonstrates the advantage that the present claimed invention provides with respect to the prior art. The prior art, and in particular Suzuki, does not contain any information which teaches or suggests the fact that benzamide derivatives may be unstable in pharmaceutical formulations or that would differentiate the desired formulations represented by c, d, e and f versus the less desired formulations represented by b, g, h, and i. Further, Suzuki does not address the problem of degradation at any point. Clearly then, Suzuki also does not provide any suggestion to a person of ordinary skill in the art as to how this problem may be solved. Moreover, Suzuki does not even generally mention use of amino compounds and does not disclose the specific combination of benzamide derivative, an excipient, a lubricant, a disintegrant, and an amine compound and/or inorganic base. As such, knowledge of the increased stability of a benzamide derivative in the formulations according to the present invention together with the specific combinations of additives as claimed in new claim 44 is unexpected and could not be derived by a person of ordinary skill in the art based on a reading of Suzuki alone or in combination with the Dictionary.

Example 4 of the present application (page 13, line 25 to page 15, line 8) relates to pharmaceutical formulations as claimed in new independent claim 46. In particular, the "claimed samples" include those tested in Example 4 which contain a benzamide derivative of formula (1), a solvent and at least one member selected from an organic acid salt, an amino compound and an inorganic base. As is evident from Table 6 at page 15, these formulations exhibit a higher stability (expressed through a lower percentage of degradation products) than the comparative control sample, which in addition to the benzamide derivative only contains a solvent, but no further additive. Thus, benzamide derivative formulations as generally claimed in new claim 46 are superior to previously known formulations with respect to their stability against degradation. As discussed above, Suzuki does not address the problem of degradation of benzamide derivative formulations, let alone provide hints or suggestions to a person of ordinary skill in the art as to how this problem could be solved. Suzuki does not teach or suggest that, in addition to a solvent, the use of an organic acid salt, an amino compound and/or an inorganic base is needed to stabilize the benzamide derivative. Therefore, the increased

stability of the pharmaceutical formulation according to new claim 46 could not have been expected by a person of ordinary skill in the art based on the teaching of Suzuki alone or in combination with the Dictionary.

Furthermore, Examples 5 and 6 at pages 15 to 17 of Applicants' specification demonstrate that the specific embodiment claimed in new independent claim 46, (*i.e.*, a formulation containing the benzamide derivative and polyethylene glycol 400 as a solvent at pH in the range of about 7 to about 11) exhibits particularly good stability against degradation. The stability of such formulations is, as demonstrated in Table 7 at page 16 and in Table 8 at page 17, further enhanced with respect to comparable formulations that have a pH value which is either above or below the range of about 7 to about 11. Again, this enhanced stability of the pharmaceutical formulation according to the present application could not have been expected by a person of ordinary skill in the art based on the teaching of Suzuki alone or in combination with the Dictionary.

The above discussion of the patentability of Applicants' new claims also applies to new dependent claim 49, which recites the benzamide derivative of formula (3).

For at least the above stated reasons, Applicants assert that the subject matter of new claims 44-49 is both novel and nonobvious over the teachings of Suzuki alone or in combination with the Dictionary.

2. Conclusion

Upon consideration of the foregoing, it will be recognized that Applicants have fully and appropriately responded to all of the Examiner's rejections. Accordingly, all claims are believed to be in proper form in all respects and a favorable action on the merits is respectfully requested. The Examiner is invited to contact the undersigned with any questions or concerns that may prevent this requested allowance.

Except for issues payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **constructive petition for extension of time** in accordance with 37 C.F.R. 1.136(a)(3).

Respectfully submitted,
Morgan, Lewis & Bockius LLP

Dated: **December 9, 2005**
Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: 202-739-3000
Fax: 202-739-3001

Gregory T. Lowen
Registration No. 46,882
Direct: 202-739-5915